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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/049,379
Filing Date: February 12, 2002
Appellant(s): IBRAHIM ET AL.

Duane M. Byers
Registration No. 33,363
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 17, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-11 and 15-17 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,716,988	IBRAHIM et al.	02-1998
5,897,871	SCHLIPALIUS	04-1999
4,439,181	BLACKSHEAR et al.	03-1984

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

- Claims 1-11 and 15-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ibrahim *et al.* (US 5,716,988) in view of Schlipalius (US 5,897,871). This rejection is set forth in a prior Office Action, mailed on 06/17/04.
- Upon further consideration, the 35 U.S.C. §103(a) rejection of Claims 1-11 and 15-17 as being unpatentable over Ibrahim *et al.* (US 5,716,988) in view of Blackshear *et al.* (US 4,439,181) has been *withdrawn*. Accordingly, the only

pending rejection applicable to the appealed claims is the 35 U.S.C. §103(a) rejection of claims 1-11 and 15-17 over Ibrahim *et al.* (US 5,716,988) in view of Schlipalius (US 5,897,871).

Claims 1-11 and 15-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ibrahim *et al.* (US 5,716,988) in view of Schlipalius (US 5,897,871).

Ibrahim *et al.* teach a solution of oxaliplatinum and water for administration through injection of infusion (see reference column 2, lines 9-19). The concentration of the oxaliplatinum is from 1 to 5 mg/ml (col. 2, lines 9-19). The solution can be sealed in a vial infusion pouch, an ampoule or carried in an injection micropump (col. 2, lines 54-63). The method of preparation is recited in Example 1 at Column 3. Ibrahim *et al.* do not expressly teach the exact concentration for the oxaliplatinum nor does the reference teach other solvents for the solution.

Schlipalius teaches that active agents can be in solution with glycerol and can be administered by injection or infusion (col. 7, claims 1-5; and col. 3, line 15 – col. 14, line 36).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to use a suitable solvent to prepare injection or infusion solution for administration that includes oxaliplatinum and glyercol in differing concentrations.

While the reference does not teach the complete concentration range, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). The Examiner does not see the criticality in the particular concentrations for oxaliplatinum compound. The prior art teaches the compound to have the same activity in a concentration close of the claimed concentration. Any difference is a matter of degree and not of kind.

One of ordinary skill in the art would have been motivated to do this to prepare a pharmaceutically active solution that implements a solution that is non-toxic, is a normal component of human and animal tissues and plasma, and maintains the fluidity of the solution without loss of the biological activity.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(11) Response to Argument

- With respect to Claim 1, Appellant argues, "Applicants have surprisingly discovered that oxaliplatinum at the claimed concentration (at least 7 mg/ml) and claimed solvent provides an unexpected stability in a wide range of utilization temperatures. This novel and non-obvious preparation is clear, colorless and free of precipitate and remains in this stable form for an extended duration of time.

The Ibrahim reference actually teaches away from the claimed invention. In particular, Ibrahim describes a pharmaceutical preparation of oxaliplatinum wherein the oxaliplatinum is dissolved in water in a concentration in the range from 1 to 5 mg/ml, and preferably at a concentration of 2 mg/ml. The secondary references of Schlipalius and Blackshear do not overcome the deficiencies of the primary reference. Schlipalius does not describe or suggest any composition or method leading to a pharmaceutically stable preparation of oxaliplatinum as claimed in claim 1. There is no motivation or suggestion in either the primary reference or secondary reference to combine these two references and end up with the claimed invention. To modify the primary reference would run contrary to the express teachings of the primary reference and confirm the improper use of hindsight."

These arguments are not found persuasive. Appellant's arguments that the instant concentration range of oxaliplatinum (at least 7 mg/ml) and claimed solvent provides unexpected and surprising results of stability is not persuasive since the prior art clearly teaches and suggests an oxaliplatinum preparation that provides for stability and achieves this stability over a pharmaceutically acceptable duration of *3 to 5 years* at room temperature or at the temperature of a refrigerator (see Ibrahim '988 column 2, lines 23-34). Evidence of this stability is also demonstrated in Example 3, at columns 3-4, wherein stability tests were conducted on aqueous solutions of oxaliplatinum. The results demonstrate that 'under all the experimental conditions

used, the stability of the aqueous solution of oxaliplatinum can be considered as pharmaceutically acceptable. Further, the solutions remained optically pure (no isomerization).' Appellant argues that the 'instant novel and non-obvious preparation is clear, colorless and free of precipitate and remains in this stable form for an extended duration of time'. In response, the Examiner points out that the prior art also teaches that the 'initial content and the solution remains *clear, colorless and free of any precipitate* after storage of a pharmaceutically acceptable duration' (see col. 2, lines 9-19 & col. 4, lines 35-36). The prior art also teaches that the oxaliplatinum preparation is administered by the parenteral route, as similarly desired by the Applicant (see col. 1, line 66 – col. 2, line 8). Appellant's argument that 'Ibrahim uses oxaliplatinum at a concentration ranging from 1 to 5 mg/ml, and preferably at a concentration of 2 mg/ml' is not persuasive. Admittedly, while the prior art teaches a concentration range of oxaliplatinum from 1 to 5 mg/ml, and preferably 2 mg/ml, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In the instant case, no criticality has been observed in the claimed concentration range of at least 7 mg/ml since the primary reference expressly desires and achieves the objective of obtaining a pharmaceutically stable oxaliplatinum, which is stable for an acceptable duration of time and obtains an oxaliplatinum

solution, which remains clear, colorless and free of any precipitate after storage of a pharmaceutically acceptable duration (i.e., 3-5 years). In response to Appellants' argument that 'there is no suggestion or motivation to combine Schlipalius with Ibrahim', the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference of Ibrahim ('988) teaches a parenterally administered stable oxaliplatinum formulation comprising solvents and administered in a range from 1 to 5 mg/ml. Ibrahim *et al.* do not expressly teach the oxaliplatinum claimed concentration and do not teach the instant selection of solvents of instant claim 1. Schlipalius ('871) remedies this deficiency of Ibrahim *et al.* by teaching active agents administered by injection or infusion, wherein the active agents are used in solution with glycerol (see Abstract and col. 3, lines 6-8). In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from

the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

- Regarding Claim 2, Appellant argues, "There is no disclosure in the cited references to prepare a stable pharmaceutical composition wherein the oxaliplatinum is contained in a solution in the solvent at a concentration of at least 9 mg/ml and wherein 1 ml of the solvent comprises at least 100 mg of one or several of the hydroxylated derivatives."

The Examiner was not persuaded by this argument, since although the prior art teaches a lower concentration range of oxaliplatinum in a range of 1 to 5 mg/ml, the prior art, nevertheless achieves effective results of stability over an extended duration of time using the lower concentration range of 1 to 5 mg/ml. Appellants have not demonstrated any surprising and/or unexpected results that accrue from the instant concentration range of at least 9 mg/ml, wherein 1 ml of the solvent comprises at least 100 mg of one or several of the hydroxylated derivatives. The prior art clearly provides for stable, parenterally administered oxaliplatinum solutions that remain stable not only for a pharmaceutically acceptable time period, but also teaches an oxaliplatinum solution that remains stable at various given temperatures.

- With respect to Claim 3, Appellant argues, "There is no disclosure in the cited references to prepare the stable pharmaceutical composition of claim 2 and wherein the solvent further comprises water."

This argument was not found persuasive since Ibrahim *et al.* teach an aqueous solution of oxaliplatinum, wherein the oxaliplatinum is dissolved in water at a concentration range of from 1 to 5 mg/ml (col. 2, lines 9-19). The examples also demonstrate the inclusion of water with oxaliplatinum to obtain stable oxaliplatinum formulations.

- In regards to Claim 4, Applicant argues, "There is no disclosure in the cited references to prepare the stable pharmaceutical composition of claim 4 wherein the oxaliplatinum concentration is between 10 and 15 mg/ml. This concentration is 100 to 200% greater than the maximum concentration taught in the primary reference and 500-750% greater that the suggested concentration in the primary reference and the solvent system is different."

This argument is not persuasive. While the prior art teaches an oxaliplatinum concentration of 1 to 5 mg/ml and does not teach that the oxaliplatinum concentration is between 10 and 15 mg/ml, it is the position of the Examiner that such optimal ranges could be routinely determined by one of ordinary skill in the art through the use of routine or manipulative experimentation to obtain the best

possible results, as these are indeed variable parameters within the art. The instant concentrations appear to be merely random selections of concentrations, which do not impart any novel results over the art of record. The prior art clearly teaches and obtains pharmaceutically stable formulations of oxaliplatinum utilizing lesser, yet effective, concentrations of the active ingredient, as compared with the present invention. Moreover, dosage concentrations administered would be dependent on various distinct factors, such as dosage per body weight, mass, gender, age, medical history and the like. Furthermore, if higher dosage concentrations were desired (*i.e.*, 10-15 mg/ml), such as claimed by Appellants, then the option of taking repeated dosages would also be possible and could be determined by one skilled in the pharmaceutical art. Regarding the distinct solvent system argued by Appellant, the secondary reference of Schlipalius ('871) teaches that solvents such as glycerol can be used in parenteral drug formulations and therefore supplies ample motivation to employ glycerol solvents in the oxaliplatinum formulation of Ibrahim *et al.* ('988).

- With respect to Claims 5-9 and 15-17, Appellant argues, "There is no disclosure in the cited references to prepare the claimed stable pharmaceutical composition and package or place them in the specific devices covered by these claims and that would maintain the composition's stability."

The Examiner was not persuaded by this argument. Instant claims 5-9 and 15-17 are directed to packaged forms such as multidoses flask, syringe, soft perfusion bag and ampoule. Ibrahim *et al.* explicitly teach an oxaliplatinum preparation packaged in containers of various forms, such as closed vials, a flexible pouch for infusion, an ampoule and an infusion device carrying an injection micropump (see column 2, lines 54-63 & Claims 4-9). Moreover, it is the position of the Examiner that marketing and packaging of drug formulations are secondary considerations that cannot be used as primary reasons to establish patentability over the art.

- Regarding Claim 10, Appellant argues, "There is no disclosure in the cited references to prepare the claimed stable pharmaceutical composition containing oxaliplatinum in a solvent at a concentration of at least 7 mg/ml and mixing the oxaliplatinum with a solvent comprising a sufficient quantity of at least one hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol."

This argument has been considered, but is not persuasive since, as delineated above, the prior art teaches stable, parenteral oxaliplatinum preparations that remain stable over extended durations and remain stable at various temperatures. The formulations also remain clear, colorless and free of precipitate after storage of a pharmaceutically acceptable duration. While the amounts taught in the prior

art are slightly lower (1 to 5 mg/ml) than those claimed, the prior art nevertheless achieves superior stability. Appellants have therefore not demonstrated any unusual or unexpected results that accrue from the instantly claimed amounts. Additionally, one skilled in the art can routinely determine suitable amounts as these are variable parameters. Moreover, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Appellants have not demonstrated any criticality in the instant amounts. The prior art expressly teaches and suggests compositions comprising the same active ingredient (*i.e.*, oxaliplatinum), administered through the same route (parenteral), used for the same field of endeavour (cancer therapy) to obtain the same objective results (stability) as that desired by Appellants.

- Lastly, regarding Claim 11, Appellant argues, "It depends from Claim 10 and includes various temperature and processing conditions that are nowhere found in the cited results."

This argument is not persuasive. The prior art teaches oxaliplatinum formulations that have an end result of stability achieved at various temperatures over an extended duration of time (see col. 2, lines 26-34 and Examples). Temperature and processing conditions are variable parameters that can be routinely determined by one skilled in the art. It is deemed obvious to modify conditions, such as temperatures, to obtain

optimal results with minimum adverse effects. Therefore, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Humera N. Sheikh 2/7/05

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February 6, 2005

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